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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,651	09/26/2005	Remu B Lal	6395-67675-06	8346
46135 7590 04/07/2008 KLARQUIST SPARKMAN, LLP 121 S.W. SALMON STREET SUITE 1600 PORTLAND, OR 97204				
EXAMINER				
KINSEY WHITE, NICOLE ERIN				
ART UNIT		PAPER NUMBER		
1648				
MAIL DATE		DELIVERY MODE		
04/07/2008		PAPER		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

**Application No.**

10/550,651

**Applicant(s)**

LAL ET AL.

**Examiner**

NICOLE KINSEY WHITE

**Art Unit**

1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 08 January 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-28 is/are pending in the application.
- 4a) Of the above claim(s) 9-11, 14-16, 18-21 and 24-28 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 17, 22 and 23 is/are allowed.
- 6) ☒ Claim(s) 1-8, 12 and 13 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Election/Restrictions***

In the reply dated, January 8, 2008, applicants argue that the claims of Groups II and III should be rejoined.

According to section 821.04 of the MPEP, the propriety of a restriction requirement should be reconsidered when all the claims directed to the elected invention are in condition for allowance, and the nonelected invention(s) should be considered for rejoinder.

Because all of the claims of the elected invention are not in condition for allowance, rejoinder of any non-elected claims will not be considered at this time.

### ***Claim Objections***

Claim 1 is objected to because of the following informalities: Claim 1 recites the term “polypeptide” twice in line 1. Appropriate correction is required.

### ***Maintained Rejections***

#### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 8, 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Hanke et al. (WO 01/47955).

The claims are drawn to an isolated recombinant polypeptide comprising a plurality of amino acid segments from one or more HIV-1 proteins, wherein two adjacent amino acid segments are linked by a spacer peptide, and wherein the amino acid segments comprise epitopes selected to be at least 50% sequence conserved across a plurality of HIV-1 subtypes.

Hanke et al. teaches polypeptide polypeptides comprising HIV CTL epitopes (see Abstract and Summary). The epitopes are conserved sequences from one or more HIV clades (see page 7, 3<sup>rd</sup> full paragraph and Table 1 on page 16). The epitopes can have spacers between each epitope or between groups of epitopes (see pages 5-6). Hanke et al. further discloses compositions of the immunogen and additional components such as pharmaceutically acceptable carriers and adjuvants (see page 8).

### ***Response to Arguments***

In the reply dated January 8, 2008, applicants argue that Hanke et al. does not teach one of skill in the art to select epitopes that are at least 50% sequence conserved. This argument has been fully considered but is not found persuasive.

As outlined above, Hanke et al. discloses the claimed invention. Hanke et al. teaches that epitopes conserved from one or more HIV clades should be used in the polypeptide. Page 7, 3<sup>rd</sup> full paragraph, states "[p]referably however, the synthetic polypeptide is large enough, and the CTL epitopes appropriately selected, such that an immune response which is cross-reactive against different HIV clades will be stimulated.

This can conveniently be achieved by including one or more CTL epitopes which are conserved among different HIV clades. Several such epitopes are known to those skilled in the art (see Table 1 below)." Hanke et al. also provides a table of HIV epitopes that are conserved across HIV clades. For example, the sequence VIYQYMDDL is 100% sequence conserved in 90% of sequenced HIV clade isolates A, B, C, D, F, G and H. In fact, all of the sequences in Table 1 are 100% sequence conserved in either 50% (lower case) or 90% (upper case) of sequenced HIV clades (i.e., the epitope sequences listed are found in 50% or 90% of sequenced HIV clade isolates A, B, C, D, E, F, G or H).

Therefore, because Hanke et al. discloses each limitation of the claimed invention, Hanke et al. anticipates the claimed invention.

### ***Claim Rejections – 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanke et al. as applied to claims 1, 2, 8, 12 and 13 above, and further in view of Velders et al. (The Journal of Immunology, 2001, 166: 5366-5373), Lopalco (U.S. Patent Application No. 2003/0003440) and Carbone et al. (Journal of Immunology, 1987, 138(6):1838-1844).

The claims are drawn to the polyepitope polypeptide further comprising a targeting signal or amino acid segments from one or more HIV-1 co-receptors or a tri-amino acid peptide spacer such as KAA or PGP.

The teachings of Hanke et al. are outlined above. Hanke et al. does not teach a targeting signal, epitopes from a coreceptor or a tri-amino acid peptide spacer.

However, Velders et al. discloses the use of an ubiquitin targeting signal to enhance processing of a polyepitope polypeptide HPV vaccine. Velders et al. found that "ubiquitination of proteins results in increased proteolysis. Since this is a proteasome-mediated pathway, ubiquitination will increase peptide presentation by the host cells." (see pages 5370 and 5372). Velders et al. further reports the induction of a CTL response and increased CTL precursor frequencies for the vaccines containing ubiquitin at the carboxyl terminus (see discussion). Lopalco teaches the use of CCR5 epitopes to induce antibodies against CCR5 and the use the antibodies to prevent or inhibit HIV infections. With regard to the tri-amino acid spacer, it is well known in the art

Art Unit: 1648

to use spacers, in particular tri-amino acid spacers, between epitopes (see Velders et al., which used a AAY spacer between epitopes and groups of epitopes, see Figure 1). In addition, Carbone et al. discloses the use of the PGP tri-peptide as a linker in T cell epitopes of a cytochrome c protein (see, for example, page1841).

It would have been obvious to one of ordinary skill in the art to modify the polypeptide taught by Hanke et al. to include an ubiquitination signal. One would have been motivated to do so given the suggestion by Velders et al. that ubiquitination increases proteolysis and ubiquitination induced CTL responses and increased CTL precursor frequencies for the vaccines containing ubiquitin at the carboxyl terminus. There would have been a reasonable expectation of success given the fact that Velders et al. successfully used ubiquitin as part of a HPV vaccine.

It would have been obvious to one of ordinary skill in the art to also modify the polypeptide taught by Hanke et al. to include one or more known epitopes from an HIV co-receptor (CCR5 or CXCR4) binding site. One would have been motivated to do so given the suggestion by Lopalco that antibodies against HIV co-receptor epitopes could block infection (see, for example, paragraph [0004]), and there would have been a reasonable expectation of success given the teachings and findings of Lopalco.

It would also have been obvious to one of ordinary skill in the art to substitute any of the known spacers, in particular tri-peptide spacers as taught by Velders et al. and Carbone et al., in the construct taught by Hanke et al. and the results would have been predictable.

Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

### ***Response to Arguments***

In the reply dated January 8, 2008, applicants argue that Hanke et al. does not teach the selection of epitopes that are at least 50% sequence conserved across a plurality of HIV-1 subtypes. This argument has been address above.

Claims 1-8, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woodberry et al. (Journal of Virology, 1999, 73(7):5320–5325) in view of Suhrbier, (Expert Rev. Vaccines, 2002, 1(2):207-213), Velders et al. (The Journal of Immunology, 2001, 166: 5366–5373), Lopalco (U.S. Patent Application No. 2003/0003440) and Carbone et al. (Journal of Immunology, 1987, 138(6):1838-1844).

Woodberry et al. teaches a polyepitope polypeptide of HIV conserved CTL epitopes from various HIV proteins. The epitopes are conserved over multiple clades (see reference 2 (Brander and Walker) of Woodberry et al., which lists known HIV CTL epitopes and the HIV subtype where each epitope is found [www.hiv.lanl.gov/content/immunology/tables/ctl\\_summary.html](http://www.hiv.lanl.gov/content/immunology/tables/ctl_summary.html)).

Woodberry et al. does not teach use of spacers, a targeting signal, epitopes from a coreceptor or a tri-amino acid peptide spacer.

However, Velders et al. discloses the use of an ubiquitin targeting signal to enhance processing of a polyepitope polypeptide HPV vaccine. Velders et al. found



that "ubiquitination of proteins results in increased proteolysis. Since this is a proteasome-mediated pathway, ubiquitination will increase peptide presentation by the host cells." (see pages 5370 and 5372). Velders et al. further reports the induction of a CTL response and increased CTL precursor frequencies for the vaccines containing ubiquitin at the carboxyl terminus (see discussion). Lopalco teaches the use of CCR5 epitopes to induce antibodies against CCR5 and the use the antibodies to prevent or inhibit HIV infections. With regard to the tri-amino acid spacer, it is well known in the art to use spacers, in particular tri-amino acid spacers, between epitopes (see Velders et al., which used a AAY spacer between epitopes and groups of epitopes, see Figure 1). In addition, Carbone et al. discloses the use of the PGP tri-peptide as a linker in T cell epitopes of a cytochrome c protein (see, for example, page 1841).

It would have been obvious to one of ordinary skill in the art to modify the polypeptide taught by Woodberry et al. to include a spacer and an ubiquitination signal. One would have been motivated to do so given the suggestion by Suhrbier that the "immunogenicity of individual epitopes might be enhanced by adding appropriate amino acids between the minimal epitopes to improve their proteolytic processing and therefore immunogenicity" and the suggestion by Velders et al. that ubiquitination increases proteolysis and ubiquitination induced CTL responses and increased CTL precursor frequencies for the vaccines containing ubiquitin at the carboxyl terminus. There would have been a reasonable expectation of success given the fact that Suhrbier successfully used spacers and Velders et al. successfully used spacers and ubiquitin as part of their vaccine constructs.

It would have been obvious to one of ordinary skill in the art to also modify the polypeptide taught by Woodberry et al. to include one or more known epitopes from an HIV co-receptor (CCR5 or CXCR4) binding site. One would have been motivated to do so given the suggestion by Lopalco that antibodies against an HIV co-receptor could block infection (see, for example, paragraph [0004]), and there would have been a reasonable expectation of success given the teachings and findings of Lopalco.

It would also have been obvious to one of ordinary skill in the art to substitute any of the known spacers, in particular tri-peptide spacers, in the construct taught by Hanke et al. and the results would have been predictable.

Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

### ***Response to Arguments***

In the reply dated January 8, 2008, applicants argue that Woodberry et al. does not teach or suggest to one of ordinary skill in the art to select epitopes that are at least 50% sequence conserved across a plurality of HIV-1 subtypes. This argument has fully considered but is not found persuasive.

As outlined above, the combination of references discloses the claimed invention. The polypeptide of Woodberry et al. contains epitopes that are 100% sequence conserved across more than one HIV clade (see listing of epitopes of Brander and Walker).

***Allowable Subject Matter***

Claims 17, 22 and 23 are free of the prior art and are allowable.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **NICOLE KINSEY WHITE** whose telephone number is (571)272-9943. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1648

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nicole Kinsey White, PhD/  
Examiner, Art Unit 1648

/Stacy B Chen/  
Primary Examiner, Art Unit 1648

**Application Number****Application/Control No.**

10/550,651

**Applicant(s)/Patent under  
Reexamination**

LAL ET AL.

**Examiner**

NICOLE KINSEY WHITE

**Art Unit**

1648